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EDITORIAL

Are salmeterol's beneficial effects on corticosteroid action in the airways executed at the epithelial barrier?

Key words: airway epithelium, asthma, chronic obstructive pulmonary disease, inflammation.

Abbreviations: COPD, chronic obstructive pulmonary disease; FP, fluticasone propionate; ICS, Inhaled corticosteroids; LABA, long-acting β 2-agonists.

Asthma and chronic obstructive pulmonary disease (COPD) are both chronic inflammatory respiratory disorders with a worldwide increase in incidence. Inhaled corticosteroids (ICS) are the cornerstone of asthma treatment due to their broad anti-inflammatory spectrum. They are effective in the majority of asthma patients, although approximately 10% of asthma patients are insensitive to ICS and fail to respond even when higher ICS doses are given. Furthermore, ICS are relatively ineffective in suppressing the inflammatory response in COPD, although they effectively reduce COPD exacerbations and have been suggested to reduce lung function decline, at least in a subset of COPD patients, as reported by the Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease study.¹

Interestingly, combined treatment with long-acting β 2-agonists (LABA) has been shown to improve the beneficial effects of ICS in respiratory disease. In asthma, ICS are especially effective when used in combination with LABA,² and the addition of LABA is more effective in improving symptoms and lung function and reducing the exacerbation numbers than doubling the dose of ICS.³ Furthermore, several studies have reported that ICS/LABA combination therapy is more effective than ICS monotherapy in improving symptoms and lung function in COPD. For example, a 3-month combination treatment with fluticasone/salmeterol significantly reduced inflammation in bronchial biopsies of patients with COPD, whereas no significant effects of fluticasone monotherapy were observed on airway inflammation.⁴

The mechanism underlying the clinical observation that combined treatment with LABA improves the anti-inflammatory effects of ICS is not completely clear. LABA have been proposed to enhance corticosteroid-induced gene transcription by promoting nuclear translocation of the glucocorticoid receptor and its binding to glucocorticoid response elements in anti-inflammatory genes, for example, in airway epithelium.⁵ Additionally, LABA have been suggested to enhance the anti-inflammatory effects of ICS by extending the duration of action of ICS,² as the currently used ICS have a relatively short duration of action. Although salmeterol and fluticasone propionate (FP) have a tendency to form particle

agglomerations within the inhaler, salmeterol does not likely extend the duration of FP actions by pharmacodynamic and/or pharmacokinetic interactions between the two drugs.⁶

In the current issue of *Respirology*, Haghi and co-workers propose that salmeterol increases the anti-inflammatory effects of ICS by increasing the residence time of FP at the airway epithelium.⁷ Their study shows for the first time that salmeterol prolongs the transport of FP across the epithelial cell layer following co-deposition of salmeterol and fluticasone particles on air-liquid interface cultured lung Calu-3 cells. Haghi *et al.* suggest that salmeterol may do so by improving epithelial barrier function.⁷ The deposition of salmeterol alone or in combination with FP resulted in increased transepithelial electrical resistance during the time course of the experiment, which was not the case for FP alone. This way, salmeterol may increase the residence time of FP in the airways, resulting in a prolonged anti-inflammatory action of FP.

The findings of Haghi *et al.*⁷ are of particular interest given the pro-inflammatory role of the airway epithelial barrier in respiratory disease. The airway epithelium forms the first barrier against environmental insults, including cigarette smoke, pollutants, allergens and pathogens. In addition to its physical barrier function, airway epithelium plays a role in the innate immune defence and is a source of pro-inflammatory cytokines, especially when damaged.⁸ Abnormal epithelial damage and repair is thought to contribute to the pathogenesis of asthma and COPD,⁸ and both cigarette smoke and aeroallergens impair airway epithelial barrier function.^{8,9} Emerging evidence suggests that, at least for asthma, these events at the epithelial surface play a critical role in the development of the disease.⁸ Reduced airway epithelial barrier function is accompanied by the release of pro-inflammatory mediators.⁸ Thus, by improving epithelial barrier function, salmeterol may not only enhance the suppressive effect of ICS on the production of pro-inflammatory mediators,² but also exert anti-inflammatory effects itself by dampening the release of epithelial pro-inflammatory mediators. In addition to an increased inflammatory response, the loss of epithelial barrier function may lead to enhanced growth factor release and cross-talk between the epithelium and underlying structural cells, driving airway remodelling.⁸ Thus far, the combined effect of ICS and LABA on airway remodelling has not been studied extensively. However, Hoshino and Ohtawa have recently shown that the combination of budesonide and formoterol is more effective

than budesonide monotherapy in reducing airway wall thickness and inflammation in asthma patients.¹⁰ Still, further studies are required to investigate whether the effects of combined treatment on inflammation can be separated from effects on airway wall thickness. Furthermore, it remains to be established whether formoterol exerts similar effects as salmeterol on epithelial barrier function, and whether this would lead to similar effects on the transport of budesonide as was the case for FP. The latter is of specific interest, given the different chemical properties of FP and budesonide. Haghi and co-workers mention that their results are in agreement with previous clinical findings, showing that FP is present for a longer time in sputum than budesonide. However, they did not compare the effects on FP and budesonide in their assays. Budesonide is less lipophilic than FP, leading to a faster dissolution rate and a shorter retention time in the lining fluid of the lungs. On the other hand, budesonide may permeate slower through epithelial layers than FP, as budesonide was shown to conjugate to fatty acids in epithelial Calu-3 cells, resulting in prolonged intracellular retention.¹¹ In addition to studying the effect of LABA on the transepithelial transport of budesonide, it will be of importance to assess the effects in a clinically more relevant setting, using primary bronchial epithelial cells. Given the abnormalities in airway epithelial barrier function in asthma and possibly also COPD, studying effects on diseased epithelial cells will particularly be of interest. Nevertheless, Haghi *et al.*⁷ refer to *in vivo* data that are in line with their current findings, suggesting that the primary site of beneficial effects of salmeterol is indeed the lung epithelium. Together, the airway epithelial barrier seems a plausible target for the beneficial effects of salmeterol, decreasing epithelial permeability and transepithelial transport, thus contributing to the improvement of the anti-inflammatory actions of ICS.

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